The changing scope of colorectal cancer

C Richard Boland
Thomas Savides

Department of Medicine and Cancer Center
University of California, San Diego, Medical Center
San Diego, CA 92093

Correspondence to:
Dr Boland
crboland@ucsd.edu

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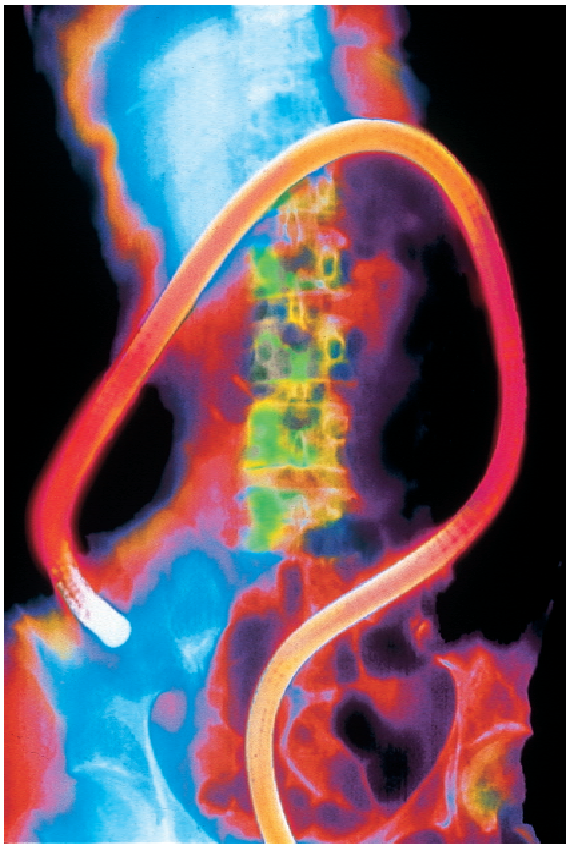
The prognosis in colorectal cancer depends on the stage at which the disease is diagnosed. Patients with advanced disease usually die of cancer, but when large intestinal tumors are found at an early asymptomatic phase, a cure can be anticipated. Furthermore, the premalignant lesions—adenomatous polyps—grow in the colon for years and perhaps decades before malignant conversion occurs, providing an opportunity for their removal and the interruption of the natural history of these neoplasms. It has long been recognized that preventive strategies would be appropriate for this disease, and an extensive literature can be found on the subject.

Two general approaches to detecting asymptomatic early-stage colorectal cancers have been studied in depth. The first is the use of fecal occult blood tests because colorectal neoplasms add blood to the stool that can be detected before the development of symptoms. However, this approach is relatively weak because of deficiencies in both sensitivity and specificity. One can expect a reduction of colorectal cancer mortality of less than 20% if the test is performed every other year.[1-3] False-positive tests greatly outnumber true-positives, all of which require a full investigation. The test is easy and noninvasive, but compliance is poor. This approach is often used, but enthusiasm for it should be limited. The second approach is to perform endoscopic screening on asymptomatic individuals and remove the premalignant lesions. Although all of the evidence for efficacy of the latter approach is either retrospective or uncontrolled, the reduction in cancer mortality might be as high as 70% to 80%, and it may be sufficient to perform these examinations only once every 5 to 10 years to achieve this outcome.[4,5]

Flexible sigmoidoscopy will readily detect neoplasms as far as the splenic flexure in unsedated patients. The traditional autopsy-based literature from the mid-20th century indicated that as many as 75% of all colorectal neoplasms occurred in the distal colon. With this distribution, sigmoidoscopy would be an excellent (though imperfect) means of finding early colorectal cancers. However, if the distribution of colorectal lesions should shift, the effect of this procedure would change accordingly. It has been reported from North America and Europe that in the past several decades, the location of colorectal neoplasms is shifting from the left to the right side of the colon. McCallion et al have communicated that when the distribution of colorectal cancers in Northern Ireland reported



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Colonoscopy allows full examination of the colon when screening for colorectal cancer

from 1990 to 1997 was compared with those reported from 1976 to 1978, a significant proximal shift had occurred; whereas only 23.5% of cancers were found proximal to the splenic flexure in the early time period, this number grew to 36.7% in the 1990s.[6] Is this really the case, and if so, what accounts for it?

First, did this apparent proximal shift really occur, or was it an artefact of data collection? It is possible that previously undercounted proximal cancers are more accurately diagnosed by the use of current technology, including colonoscopy and imaging techniques. One would need to know how often patients died without an accurate diagnosis of a proximal colon cancer in the 1970s, and this may be difficult or impossible to learn. The number of deaths in the Northern Ireland registries that were attributed to abdominal cancer of unknown source has probably fallen, and the assumption is that proximal rather than distal cancers would have more likely been undiagnosed. It is perhaps worth noting that the two databases used by McCallion et al had substantial differences in ascertainment: the Northern Ireland Cancer Registry (NICR) reported 922.3 colorectal cancers per year whereas the Northern Ireland CRC registry reported only 644.1 per year, as pointed out by the authors.[6] They have rejected a significant effect of these differences, but in the NICR database, nearly 20% of colorectal cancers were of an unknown site.

Second, if this pattern shift is true, what is the mechanism for this change? A growth in public awareness of symptoms and prompt diagnosis of symptomatic cancers may lead to a reduction in mortality, but not in cancer incidence, which would remain unchanged. If a substantial proportion of the population had been subjected to screening sigmoidoscopy with the attendant removal of adenomas, this might lead to a substantial reduction in cancer incidence, especially in the distal colon and rectum. The authors do not present data on the frequency of flexible sigmoidoscopy for colon cancer screening during the two periods, but it is possible that there had been an increased use of flexible sigmoidoscopy (for screening or symptoms) during the 1990-1997 period compared with the 1976-1978 period. Such has been the case in the United States. If the later study group consisted of a more elderly population, it is expected that there would be a greater proportion of proximal colon cancers.[7] Finally, perhaps another factor has intervened to alter the distribution of cancers within the colon. It has been demonstrated that aspirin and nonsteroidal anti-inflammatory drug users experience a reduction in cancer mortality in the range of 40%, even for relatively occasional users.[8,9] If additional factors such as increased caloric intake raised the general risk for cancer in the population and aspirin and related agents reduced the risk in the distal colon, there would appear to be a left-to-right shift at the population level. This remains conjecture at present, but it is likely that the factors responsible for the pathogenesis of proximal cancers may be different from those that lead to distal cancers.

Finally, what is the clinical effect of a true shift in colorectal neoplasms toward the proximal colon? Recent publications from North America explore the effect of screening with total colonoscopy.[10,11] A substantial number of patients have important lesions above the reach of the sigmoidoscope without distal "signal" lesions. Patients in the United States have access to this information through the news media and the Internet and increasingly are insisting on a complete colonoscopic examination, particularly if they perceive themselves to be at an increased risk for cancer. Considerable investment of resources are at stake in this debate. Perhaps we should accept that only a full examination of the colon will suffice for purposes of screening. This would add pressure to more fully develop highly accurate noninvasive imaging techniques to screen the entire colon, such as virtual colonoscopy. Eventually genetic testing of stools might be sufficiently sensitive to act as a primary screening test.[12] We have come a long way since the first stool specimen was tested with guaiac reagents. We need to adapt to the changing nature of the

disease that might be occurring as we design optimal prevention programs.

References

1 Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472-1477.
2 Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467-1471.
3 Mandel JS, Church TR, Bond JH, et al. The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000;343:1603-1607.
4 Selby JV, Friedman GD, Quesenberry CP Jr, Weiss NS. A case-control study of screening sigmoidoscopy and mortality from colorectal cancer. *N Engl J Med* 1992;326:653-657.
5 Winawer SJ, Zauber AG, O'Brien MJ, et al. Randomized comparison of surveillance intervals after colonoscopic removal of newly diagnosed adenomatous polyps. The National Polyp Study Workgroup. *N Engl J Med* 1993;328:901-906.
6 McCallion K, Mitchell RMS, Wilson RH, et al. Flexible sigmoidoscopy and the changing distribution of colorectal cancer: implications for screening. *Gut* 2001;48:449-450.
7 Saltzstein SL, Behling CA, Savides TJ. The relation of age, race, and gender to the subsite location of colorectal carcinoma [letter]. *Cancer* 1998;82:1408-1410.
8 Thun MJ, Namboodiri MM, Heath CW Jr. Aspirin use and reduced risk of fatal colon cancer. *N Engl J Med* 1991;325:1593-1596.
9 Giovannucci E, Egan KM, Hunter DJ, et al. Aspirin and the risk of colorectal cancer in women. *N Engl J Med* 1995;333:609-614.
10 Lieberman DA, Weiss DG, Bond JH, Ahnen DJ, Garewal H, Chejfec G. Use of colonoscopy to screen asymptomatic adults for colorectal cancer. Veterans Affairs Cooperative Study Group 380. *N Engl J Med* 2000;343:162-168.
11 Imperiale TF, Wagner DR, Lin CY, Larkin GN, Rogge JD, Ransohoff DF. Risk of advanced proximal neoplasms in asymptomatic adults according to the distal colorectal findings. *N Engl J Med* 2000;343:169-174.
12 Ahlquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: feasibility of a multitarget assay panel. *Gastroenterology* 2000;119:1219-1227.